REMARKS

Claims 1-4, 11-18, 20, 37-39, 42-43, 45-48 & 50 were rejected under 35 USC 112, 1st paragraph and also under 35 USC 112, 2nd paragraph. Under 35 USC 103(a), claims 1-4, 11-18, 20, 37-38, 48 & 50 were rejected as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186) in view of Morrison et al. (2001 Current Opinion in Chemical Biology 5: 304-307) and current practice in protein design as evidenced by Wells (1990 Biochemistry 29(37): 8509-8517), claims 39, 42-43 & 45-46 rejected over Arcone et al. in view of Morrison et al., current practice in protein design (Wells) and Veronese (2001 Biomaterials 22: 405-417), and claim 47 rejected over Arcone et al. in view of Morrison et al., current practice in protein design (Wells), Veronese and Roberts et al. (2002 Advanced Drug Delivery Reviews 54: 459-476).

In response, Applicants have amended claims 1-2 & 20 as Examiner suggested and canceled claim 37 to overcome the 112 (2nd paragraph) rejections, and have submitted the following remarks for the other rejections. New claims 58-60 dependent from claims 1, 2 and 20 respectively have also been added. Reconsideration of claims 1-4, 11-18, 20, 38-39, 42-43, 45-48 & 50 and consideration of new claims 58-60 are requested.

Regarding the 112 (1st para.) rejections, Applicants submit that claims 1, 2 & 20 are clear enough without defining the whole sequence, at least for thrombin is a well-known protein and serine at position 205 and histidine at position 43 of the B chain are clear to one of ordinary skill in the art, as disclosed in Arcone et al. as one prior-art reference.

Regarding the 103(a) rejections, Applicants' arguments are as follows.

The thrombin derivative of each independent claim 1, 2 or 20 features the mutations at serine at position 205 (S205), and histidine at position 43 (H43).

Arcone et al. disclose the thrombin mutants each having a single mutation such as S205T, D99N, H43N, S205A or G203A, but disclose no thrombin mutant having a double mutation at both H43 and S205. The single mutants disclosed in Arcone et al. still have thrombin activity, and therefore cannot be used as antithrombotic agent.

Though Arcone et al. describe in Abstract "*Mutations S205A and G203A completely abolished the enzymatic activity*", the activity was evaluated by the assay using synthetic peptide S-2238 as a substrate (see section 2.5 of Arcone et al.). In the assay, the residual activity of the thrombin mutants cannot be detected. In fact, this application shows that G203A still has thrombin activity detectable by the assay using FXIII and fibrinogen as a substrate (Experimental Example 15 and Fig. 20). S205T also has thrombin activity detectable by the assay using FXIII as substrate (Experimental Example 4). Such mutant thrombins maintaining some thrombin activity cannot be used as an antithrombotic agent because of the side effects caused by the residual proteolytic activity of the mutants.

Moreover, single mutants disclosed in Arcone et al. have decreased binding ability to substrates such as FVIII and thrombin receptor. For example, Experimental Example 3 showed that the FVIII binding signal of S205A mutant decreased to about 40% as compared to that of AHT (anhydrothrombin). The binding ability is indispensable property for exerting the antithrombotic activity. As described in Experimental Example 3 (paragraph [0123]), the S205A thrombin mutant does not have the thrombin receptor-activating ability of a level at which the

S205A mutant can be practically used as an antiplatelet agent in plasma. The decreased binding of the S205A mutant to the substrates such as FVIII and thrombin receptor resulted in weak APTT-prolonging effect ([0123]). Other mutants also have decreased binding ability to the substrates (S205V (Example 6), S205D (Example 7), S205N (Example 8), and S205G (Example 24)), and cannot be used as an antithrombotic agent.

On the other hand, the thrombin mutants having mutations at S205 and H43 have completely lost the thrombin activity but maintained the substrate binding ability (more than that of AHT) as described in paragraphs [0145], [0152], [0172] and [0173] of this application, thereby exerting a significant APTT-prolonging effect and an antiplatelet effect to be suitably used as an antithrombotic agent.

Such effects cannot be obtained by randomly combining the single mutations taught by Arcone et al. according to the current practice in protein design (Wells). For example, G203A S205G D99N, S205A D99N, G203A S205A and G203A S205G in Experimental Examples 5, 10, 11 and 2 respectively have decreased binding ability to the substrates and little APTT-prolonging effect. Further, these mutants cannot exert the antiplatelet effect.

Moreover, Morrison et al. simply teach a general method of studying the importance of a non-alanine amino acid by substituting the amino acid with alanine (see Abstract), and either can not show an effect of combining the mutations at S205 and H43.

For at least the above reasons, one of ordinal skill in the art could have never been expected from the teachings of Arcone et al., Morrison et al., and current practice in protein design (Wells) that an excellent antithrombotic agent having a significant APTT-prolonging

effect and an antiplatelet effect can be obtained by combining the mutations at S205 and H43. The other references cited for rejecting some dependent claims, Veronese and Roberts et al., also fail to teach the above feature of the independent claims.

For at least the above reasons, amended claims 1-2 & 20 and claims 3-4, 11-18, 38-39, 42-43, 45-48, 50 & 58-60 dependent therefrom all patently define over the prior art.

CONCLUSION

For at least the foregoing reasons, it is believed that pending claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50 & 58-60 of the present application are in proper condition for allowance. Rejoining of withdrawn claims 5, 21-36, 40-41, 44, 49 & 51-57 all dependent from claim 1 is also requested if Examiner would allow claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50 & 58-60. If Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

Respectfully submitted,
J.C. PATENTS

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/JIAWEI HUANG/
Jiawei Huang
Registration No. 43,330
Email: jcpi@msn.com

4 Venture, Suite 250
Irvine, CA 92618
Tel.: (949) 660-0761
Fax: (949)-660-0809